Clinical investigation to evaluate the effectiveness of the Ambu® aScope™ 4 Cysto with the Ambu® aView™ 2 Advance for flexible cystoscopy

Clinical Investigational Plan CIS-023

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Investigational Plan Date: 08 October 2020
Version # 2

INVESTIGATIONAL PLAN SIGNATURE PAGE

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INVESTIGATOR'S AGREEMENT

By signing below, I confirm that I have read, understand, and agree to follow this clinical study investigational plan, applicable federal regulations including 21 CFR 50 and requirements imposed by the governing Institutional Review Board (IRB). I further agree to provide full oversight of all study team members at my site to assure they also adhere to this investigational plan, applicable regulations, and IRB requirements. I agree to conduct the study according to the procedures described in the clinical study investigational plan and maintain confidentiality of non-public information.

Investigational Site Name:	
Principal Investigator Name:	
Principal Investigator Signature:	
Date:	

List of Abbreviations and Acronyms

AE	Adverse Event
ASA	American Society of Anesthesiologists
AUA	American Urological Association
BMI	Body Mass Index
CFR	Code of Federal Regulations
CPT	Cumulative Procedure Time
CRF	Case Report Form
CV	*Curriculum vitae*
DAL	Device Accountability Log
DCF	Data Clarification Form
DICOM	Digital Imaging and Communications in Medicine
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EHR	Electronic Health Record
FDA	Food and Drug Administration
FPFV	First Patient, First Visit
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed Consent Form
ID	Identification
IFU	Instructions for Use
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intention to Treat
LED	Light Emitting Diode
LPLV	Last Patient, Last Visit
PACS	Picture Archiving and Communication System
PP	Per Protocol
PI	Principal Investigator
UTI	Urinary Tract Infection
SAE	Serious Adverse Event
SOC	Standard of Care
Sub-I	Sub-Investigator
TMF	Trial Master File

Investigational Plan Synopsis

Study Title and Number	Effectiveness of aScope™ 4 Cysto with the Ambu™ aView™ 2 Advance for flexible cystoscopy
Study Device	Ambu® aScope™ 4 Cysto - Single-use cystoscope with an Ambu® aView™ 2 Advance monitor for direct visualization of the urethra and bladder
FDA Clearance	K193095
Indication for Use	The aScope™ 4 Cysto is a sterile, single-use, flexible cystoscope intended to be used for endoscopic access to and examination of the lower urinary tract. The aScope™ 4 Cysto is intended to provide visualization via Ambu displaying units and can be used with endoscopic accessories. The aScope™ 4 Cysto is intended for use in a hospital environment or medical office environment. The aScope™ 4 Cysto is designed for use in adults.
Comparator	The comparator device will be the standard flexible reusable cystoscope of the urologist's choice appropriate for the removal of (a) ureteral stent(s).
Study Purpose	To evaluate the use of the single-use Ambu® aScope™ 4 Cystoscope for removal of ureteral stents as compared to routine flexible reusable cystoscopes.
Study Design	This is a prospective, randomized, two-arm post-market clinical trial.
Primary Study Objective	To demonstrate the success rate of the Ambu® aScope™ 4 Cysto and the Ambu® aView™ 2 Advance for stent removal procedures performed in the outpatient setting.
Primary Endpoint	Stent removal procedural success rate with the Ambu® aScope™ 4 Cysto and the Ambu® aView™ 2 Advance.
Secondary Objective	• To compare the Ambu® aScope™ 4 Cysto and the Ambu® aView™ 2 Advance for stent removal procedures performed in the outpatient setting to standard of care reusable scopes on scope performance. • To compare the Cumulative Procedure Time between the Ambu aScope™ 4 cysto and the site's SOC reusable flexible cystoscope.

	• To evaluate the user experience and product performance during cystoscopic procedures.
Secondary Endpoints	1. To compare the Cumulative Procedure Time between the Ambu aScope™ 4 cysto and the site's SOC reusable flexible cystoscope as measured by: a. Scope preparation for procedure b. Actual procedure time (insertion of cystoscope to removal of cystoscope) and c. Time to dispose of or prepare for reprocessing of cystoscopy equipment. 2. Clinician satisfaction, rated on a five-point scale a. Ease of insertion b. Ability to visualize anatomical landmarks and/or urothelium changes c. Perception of image quality d. Maneuverability in the bladder e. Scope articulation with tools in the working channel f. Visualization while tools are in the working channel 3. Rate of conversion to a reusable cystoscope, 4. Device deficiency rate, further categorized as either: a. Device Failure: leading to a serious adverse event (SAE), termination of the procedure, or conversion to a reusable cystoscope b. Device Malfunction: including any device-related issue or observation whether it leads to an SAE, termination of the procedure or conversion to a reusable cystoscope
Safety Objectives	To evaluate the urologic adverse events, both device and procedure related, during the cystoscopy procedure through ten (10) days post-procedure.
Safety Endpoints	Safety will be assessed based on the incidence rates of adverse events based on the seriousness and relatedness to the device and/or procedure. 1) All reported device and/or procedural related adverse events through ten (10) days post-procedure 2) All Serious Adverse Events (SAEs) through 10 days post-procedure
Study Population	Eligible subjects are adults undergoing outpatient ureteral stent removal, male and female, age ≥18 years of age.

Key Inclusion Criteria	1) Adult (male or female), ⩾18 years old 2) Patient undergoing routine flexible cystoscopy 3) Patient with a ureteral stent in the urinary system that is ready to be removed. 4) No active urinary tract infection 5) Subject is willing and able to sign informed consent and HIPAA authorization and comply with requirements of the protocol.
Key Exclusion Criteria	1) History of prior bladder/urethral reconstructive surgery. 2) History of high-grade bladder cancer or carcinoma in-situ of the bladder, undergoing cystoscopy for follow-up/surveillance purposes. 3) Known unpassable urethral stricture 4) Febrile patient with active urinary tract infection (UTI) 5) Subjects with acute infection (acute urethritis, acute prostatitis, acute epididymitis) 6) Subject with severe coagulopathy 7) Patient is unable to read and/or understand study requirements 8) Patient is unable or unwilling to provide written consent to participate in the study. 9) Subject, in the opinion of the Investigator, has a severe comorbidity, poor general physical/mental health and/or a condition that will not allow the subject to be a good study candidate.
Estimated Study Duration	It is expected that study duration will be nine (9) months from first patient, first visit (FPFV) to last patient, last visit (LPLV).
Estimated Subject Participation Time	An individual subject's participation from screening, procedure, and follow-up telephone call is anticipated to be ten (10) days.
Study Sites	Patients will be enrolled from up to four (4) outpatient urology clinics in the United States. •
Study Hypotheses	• The aScope™ 4 Cysto will perform with a 95% success rate of stent removal procedures. • The aScope™ 4 Cysto will perform comparably to SOC flexible cystoscopes for all other endpoints.
Sample Size	Up to 102 subjects will be enrolled in the study. Subjects will be randomized at a 1:1 ratio.

Statistical Methods	The primary objective of demonstrating the stent removal success rate in the aScope™ 4 Cysto arm will be measured by descriptive statistics of the success rate, including 95% confidence intervals. The null-hypothesis for all other endpoints will be that the that the value of the endpoint is equal among patients randomized to aScope™ 4 Cysto and patients randomized to the standard flexible cystoscope of the urologist's choice. All continuous variables and all ordered categorical data will be tested by means of the Wilcoxon rank sum test. Binary data will be tested by means of the Fisher's exact test. All p-values will be 2-sided and nominal p-values will be presented, i.e. no adjustment for multiplicity. Descriptive statistics, including 95% confidence intervals, will be presented by group for each variable. The assessment of safety will include a summary of the incidence and seriousness of all reported adverse events through the 10-day follow-up assessment including the following: • Rates of all reported adverse events • Rates of device-related adverse events • Rates of procedure-related adverse events
Data Analysis Sets	1) The intention to treat (ITT) analysis set will consist of all enrolled subjects regardless of whether they have undergone a stent removal procedure or completed the 10-Day follow-up assessment. 2) The per protocol (PP) analysis set will consist of all enrolled subjects who complete the stent removal procedure and 10-Day assessment. The PP analysis set will be the primary analysis set and the analyses based on the ITT analysis set will be considered sensitivity analyses.

1. Background

The principle of using a source of light and a tube to visualize the bladder and its diseases has been known for hundreds of years.[1,2] Currently, cystoscopy, defined as an endoscopy of the urinary bladder via the urethra may employ either a rigid or a flexible cystoscope and may be performed for either diagnostic or therapeutic purposes.

Flexible cystoscopy continues to improve by:

- miniaturization of the instruments, scopes and accessory devices
- improvement of the images
- addition of fluorescence technologies in the detection of malignancies
- increasing flexibility and ergonomic improvements
- focusing on improving reprocessing activities related to safety, cost and environment.

Cystoscopes are used in daily clinical practice worldwide, and cystoscopies are one of the most commonly performed medical procedures.[3] In urology flexible cystoscopes play an important role in the management of intravesical diagnostic and therapeutic activities .[2,4,5,6,7,8] Flexible cystoscopes can be programmed, and are commonly used in emergency situations, depending on the indication.[6,9] One indication for the use of a flexible cystoscope together with a grasper is the ureteral stent withdrawal.[3,4,9,10]

The diagnostic use of cystoscopy is diverse including; the evaluation of patients with voiding symptoms (storage or obstructive), gross or microscopic hematuria, evaluation of urologic fistulas, evaluation of urethral or bladder diverticula, congenital anomalies in pediatric population, retrieval of samples (for cytologic and histologic studies), intraoperative evaluation of the urethra, bladder, and ureters after some incontinence or prolapse procedures, retrograde pyelography for upper urinary tract evaluation, urethritis, diagnostic of polyps or overgrowths of normal tissue, evaluation of scarring and damage caused by frequent urinary tract infections (UTIs), injury of the urinary tract, abnormalities of the urinary tract that may be present at birth and may lead to a backflow of urine or kidney problems, diagnostic of cancer or tumor of the bladder or urethra, visualization of bladder stones, urinary tract infections, unusual cells found in urine sample.

Therapeutic use of cystoscopy includes; the treatment of urethral strictures, bladder neck procedures, intravesical procedures such as treatment of bladder stones, bladder ulcers, bladder tumors, bladder tumors biopsy, removal of foreign bodies in the bladder, botulinum toxin injection for urinary incontinence and overactive bladder, insertion of a urethral catheter using cystoscopy in difficult cases (bedside procedure), double loop (also named JJ) stent insertion or removal, removal of burst urethral catheter balloon fragments or any other foreign bodies.

The Ambu® aScope™ 4 Cysto is a sterile, single-use, flexible cystoscope intended to be used for endoscopic access to and examination of the lower urinary tract. The endoscope is intended to provide visualization via the Ambu® aView™ 2 Advance displaying unit. The working channel system allows the passage of endoscopic accessories, instillation of fluids (e.g. saline for expanding the bladder) and suctioning of fluids. The Ambu® aScope™ 4 Cysto shall be disposed as infected medical device with electronic components. The endoscope will be used for adult patients requiring cystoscopy.

The insertion cord together with the bending cover and the distal tip are inserted into the urethra meatus and lower urinary tract of the patient. It is lubricated with a water-soluble medical grade lubricant and local anesthetics, to ensure the lowest possible friction inserted into the patient. The insertion cord can be wiped with Hospital Disinfection Swab w. isopropyl alcohol/ethanol etc. The user can bend the distal tip in a single plane to obtain visualization of the lower urinary tract by sliding the bending lever up and down activating the bending section, see figure 1 and 2. The bending section is able to bend 210° (UP direction) making it possible to do retroflexion for visualizing the bladder neck and insertion cord when inside the bladder.

The Ambu® aScope™ 4 Cysto is designed to be used in a hospital environment or medical office environment. This includes out-patient clinics, patient wards, operating rooms, intensive Care Units and emergency rooms. Cystoscopes are used in conjunction with different endoscopic accessories (e.g. injection needles and biopsy forceps) and energized devices (e.g. laser and bugbee electrodes) which may lead to damage of the cystoscope; therefore, repair time is also contributing to the availability of cystoscopes.

The majority of cystoscopes currently on the market are reusable cystoscopes that need reprocessing in between use. Cross contamination is a risk related to the use of reusable scopes, therefore efficient reprocessing minimizing this risk is mandatory, especially in the light of reported "super bugs" and cross-contamination with highly resistant organisms by endoscopes in urology, as well as other therapeutic areas. The single-use concept minimizes the risk of infection or cross-contamination as well as allergic reactions (of both healthcare professionals and patients) to chemical agents used during reprocessing of the cystoscopes.[11,12]

The portability of the system allows the user to move the system to different departments and areas of the hospital (e.g. patient care departments) making it instantly availability for "out of hours" use.

2. Device Description

2.1 Study Device: Ambu® aScope™ 4 Cystoscope and Ambu® aView™ 2 Advance Monitor

The Ambu® aScope™ 4 Cysto (Model 601001000) is a sterile, single use handheld 15.4 inch long, 16.2 Fr to 18 FR diameter scope with a distal camera and two LED light sources, a bending section with 210 and 120 degrees of maneuverability, a 6.6 Fr working allows channel that allows for instillation of fluids and insertion of endoscopic accessories and a bending level in the handle that moves the distal end up and down in a single plane. The

endoscope is powered by connecting to the displaying unit. The Ambu® aScope™ 4 Cysto can be used with endoscopic accessories. The working channel system allows the passage of endoscopic accessories, instillation of fluids (e.g. saline for expanding the bladder) and suctioning of fluids. The Ambu® aScope™ 4 Cysto shall be disposed as infected medical device with electronic components.

The Ambu® aScope™ 4 Cysto is available in one size and can be operated by either the left or right hand. The optical module in the distal tip consists of a camera housing containing camera and LED light sources.

This device is marketed under FDA 510(k) Clearance K193095.

The Ambu® aView™ 2 Advance monitor is a portable 12.8-inch full HD touchscreen with reduced reflections, a large image area, upgradeable software, and wide range of connectivity including to EHRs through PACS (DICOM), high quality video output or Network access. The aScope™ 4 Cysto has gone through animal and bench testing during the final development of the cystoscope. An overview of the validation and performance studies performed in support of the Ambu ® aView™ displaying unit and aScope™ 4 Cysto in 2018 and 2019 are presented in Table 1.

Summative usability testing has been carried out by seventeen (17) urologists. The purpose of the summative usability test was to validate the voice of the customer and their experience with the use of the aScope™ 4 Cysto. There were no use errors observed during the summative usability test. All seventeen (17) respondents performed the handling tasks without committing any close calls or operational difficulties). Overall, the respondents considered the tasks to be easy or very easy on a 5 point scale (1= very difficult 5= Very easy) and assigned an average, overall ease-of-performing rating of 4.8 to setting up the system and 4.7 to operating the system.

Table 1: Summary of Validation and performance testing with aScope™ 4 Cysto in chronological order

Test type	Urinary tract model	Nr of participant	Assessment Method Acceptance Criteria	Scope assessment (1,2,3,4)*	Image Quality**	Ergonomics
In-vivo test	Female porcine model (2 female pig)	6 (1 pig per 3 doctors)	5-point Likert 90% with 3, 4 or 5 points in Likert scale	Passed for 2, 3, 4.	Passed for 5c	Passed
Bench test	Ambu made lower urinary tract male model	17	Yes/No 90% of yes must apply	1,2,3,4 passed	NA	Passed
Bench test	Resolution chart	15	The resolution at distances of 3, 75 and 100 mm must be passed by at least 90% of the test participants	NA	Passed for 5a and 5b	NA

***Abbreviations:1=Insertion of scope; 2=Navigation;3=Irrigation;4=Navigation with endoscopic accessories. **"Overview" = 5a; "Details" = 5b; "Color representation" =5c.**

2.2 Indication for Use

The Ambu® aScope™ 4 Cysto is a sterile, single-use, flexible cystoscope intended to be used for endoscopic access to and examination of the lower urinary tract. The aScope™ 4 Cysto is intended to provide visualization via Ambu® displaying units and can be used with endoscopic accessories.

The aScope™ 4 Cysto is intended for use in a hospital environment or medical office environment.

The aScope™ 4 Cysto is designed for use in adults.

2.3 Comparator

The comparative device for this two-armed study will be the SOC reusable flexible cystoscope of the practitioner's choice.

3. Study Design

3.1 Study Purpose

The purpose of this study is to evaluate the use of the single-use Ambu® aScope™ 4 Cystoscope for removal of ureteral stents as compared to routine flexible reusable cystoscopes.

3.2 Study Design

This is a prospective, randomized, dual-arm post-market clinical trial that will assess the single-use Ambu® aScope™ 4 Cystoscope for removal of ureteral stents as compared to routine flexible reusable cystoscopes.

Adult subjects who are indicated for ureteral stent removal procedures will be consented and enrolled prior to having the cystoscopic performed. Clinician (PI or Sub-I) satisfaction will be assessed within one (1) working day following all procedures. Subject follow-up will be conducted between Days 7 and 10 post-procedure via phone call or outpatient clinic visit, to collect data on adverse events.

3.3 Primary Study Objective

The primary study objective is to demonstrate the success rate of Ambu® aScope™ 4 Cysto and the Ambu® aView™ 2 Advance for stent removal procedures performed in the outpatient setting.

3.4 Primary Endpoint

The primary endpoint is the success rate of the stent removal procedures performed in the Ambu® aScope™ 4 Cysto arm.

3.5 Secondary Objective

The secondary objectives are:

- To compare the Ambu® aScope™ 4 Cysto and the Ambu® aView™ 2 Advance for stent removal procedures performed in the outpatient setting to standard of care reusable scopes on scope performance.
- To compare the Cumulative Procedure Time between the Ambu® aScope™ 4 cysto and the site's SOC reusable flexible cystoscope.

3.6 Secondary Endpoints

The secondary endpoints of this study are:

1. To compare the Cumulative Procedure Time between the Ambu aScope™ 4 cysto and the site's SOC reusable flexible cystoscope as measured by:
   a. Scope preparation for procedure
   b. Actual procedure time (insertion of cystoscope to removal of cystoscope) and
   c. Time to dispose of or prepare for reprocessing of cystoscopy equipment.
2. Clinician satisfaction, rated on a five-point scale
   a. Ease of insertion
   b. Ability to visualize anatomical landmarks and/or urothelium changes
   c. Perception of image quality
   d. Maneuverability in the bladder
   e. Scope articulation with tools in the working channel
   f. Visualization while tools are in the working channel
3. Rate of conversion to a reusable cystoscope,
4. Device deficiency rate, further categorized as either:
   a. Device Failure: leading to a serious adverse event (SAE), termination of the procedure, or conversion to a reusable cystoscope.
   b. Device Malfunction: including any device-related issue or observation whether it leads to an SAE, termination of the procedure or conversion to a reusable cystoscope.

3.7 Safety Endpoints

Safety will be assessed based on the incidence rates of adverse events based on the seriousness and relatedness to the device and/or procedure.

1) All urologic adverse events, both device and procedure related, during the cystoscopy procedure through ten (10) days post-procedure.
2) All reported device and/or procedural related adverse events through ten (10) days post-procedure
3) All Serious Adverse Events (SAEs) through ten (10) days post-procedure

3.8 Estimated Study Duration

It is expected that study duration will be twelve months from first patient, first visit (FPFV) to last patient, last visit (LPLV). An individual subject's participation is anticipated to be ten (10) days.

4. Investigational Study Sites

There will be up to four (4) sites in the United States that will participate in this study.

5. Study Population

The study population will consist of adults undergoing outpatient ureteral stent removal, male and female, age ≥18 years of age.

5.1 Inclusion Criteria

All criteria must be answered "yes" for study enrollment:

1. Male or female, aged at least 18 years old
2. Patient undergoing routine flexible cystoscopy
3. Patient with a ureteral stent in the urinary system that is ready to be removed.
4. No active urinary tract infection
5. Subject is willing and able to sign informed consent and HIPAA authorization.

5.2 Exclusion Criteria

All criteria must be answered "no" for study enrollment:

1. History of prior bladder/urethral reconstructive surgery.
2. History of high-grade bladder cancer or carcinoma in-situ of the bladder, undergoing cystoscopy for follow-up/surveillance purposes.
3. Known unpassable urethral stricture
4. Febrile patient with active urinary tract infection (UTI)
5. Subjects with acute infection (acute urethritis, acute prostatitis, acute epididymitis)
6. Subject with severe coagulopathy
7. Patient is unable to read and/or understand study requirements
8. Patient is unable or unwilling to provide written consent to participate in the study.
9. Subject, in the opinion of the Investigator, has a severe comorbidity, poor general physical/mental health and/or a condition that will not allow the subject to be a good study candidate.

6. Informed Consent

Potential study subjects must document their consent for study participation and authorization for use and disclosure of health information by signing the study-specific IRB-approved Informed Consent Form (ICF). As part of the consent process, the subject will first have the opportunity to ask questions of and receive answers from site personnel conducting the study before signing the ICF. Subjects will be considered enrolled in the study once they have signed the ICF and it has been confirmed that they meet all inclusion/exclusion criteria. A person can

only be treated under this study's investigational plan one time. The informed consent process will be documented on the electronic case report form and the subject will be given a copy of the ICF.

7. Study Procedures

7.1 Schedule of Procedures

Table 1 presents the study's schedule of procedures.

Table 1. Schedule of Study Procedures

Activity	Screening Visit Day 0	Enrollment/ Baseline Visit 1, Day 0	Final Study Visit 2 Day 10 + 0/-3 days
Informed consent	X		
Inclusion/Exclusion		X	
Demographics	X		
Medical history	X		
Randomization		X	
Record set up time for procedure:		X	
Record time for stent removal		X	
Record time to prepare scope for cleaning or disposal		X	
Rate scope performance		X	
Schedule follow-up telephone call		X	
Adverse Event Assessment			
Complete Telephone interview			X
Complete Case Report Forms (CRFs)	X	X	X

7.2 Procedure Day (Day 0)

7.2.1 Informed Consent

Potential study candidates will be consented for study participation as described in Section 6, Informed Consent. Signed informed consent may be obtained prior to the procedure day and must be obtained before any study-specific procedures are performed.

7.2.2 Inclusion/Exclusion Criteria Assessment and Enrollment

After consenting, the inclusion/exclusion criteria (Section 5) will be assessed. If the subject does not meet all inclusion/exclusion criteria, she/he will not be enrolled in

the study. Subjects are considered enrolled in the study after informed consent is obtained and it is confirmed that they meet the inclusion/exclusion criteria.

7.2.3 Randomization

After meeting the inclusion/exclusion criteria, Subjects will be randomized into one of the two study arms, singe use scope (aScope 4 Cysto) or reusable scope (SOC).

7.2.4 Demographics and Relevant Medical History

Demographic and relevant medical history information will be obtained from the subject before the stent removal procedure is attempted.

7.2.5 Pre-Procedure Activity

Individual provider experience levels (years of practice) will be documented for all participating providers.

The following information will be collected for each case in the Pre-Procedure Phase.

- Time elapsed from when the reusable or single use scope enters the room to the overall set up completion (scope is lubricated and set down).
- Time to prep scope (handling time)
    - Time of single use removal from packaging/or reusable removal from transport bin.
    - Time connections to monitor/fluids/towers are made.
    - Time of visualization test.
    - Time that the scope is lubricated and set down

Any delay with receiving the reusable scope (SOC) into the procedural room will be documented in the CRF.

7.2.6 Procedure Activity

The ureteral stent removal procedures will be performed by properly trained and experienced providers according to standard of care. The following information will be collected during the procedure phase.

- Time elapsed from scope passage through meatus until scope/stent passage out of meatus
    - For those case, time will be recorded as:
        - Time from passage through the meatus to the moment of visualization
        - Time from visualization, through scope /stent passage out of meatus

Image capture is not required under this protocol. If any images were captured during the procedure, it should be documented in the case report form.

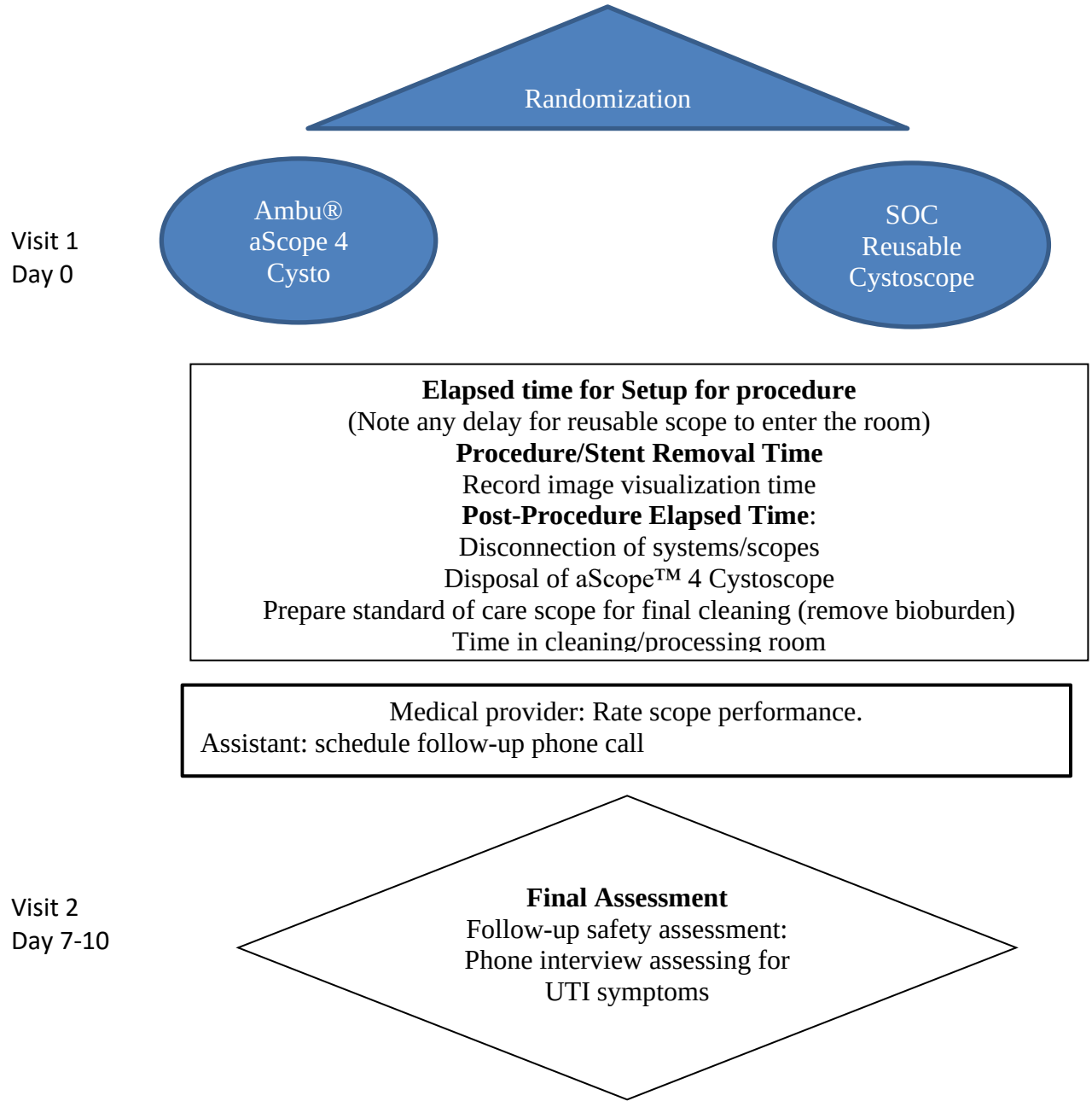
7.2.7 Post-procedure Activity

- Time elapsed from in-room decontamination/disassembly procedure, including disconnection of cables/tubing; wipe down or disposal of scope; e.g. Time elapsed from scope picked up to disposal (single use) or placement in transport bin (reusable).

As a tertiary data collection point, the following time will also be documented for the scopes evaluated:

- Time elapsed from deposition of scope in processing room until time that scope is ready for sterilization.

This process is detailed in the following flowchart:



7.2.8 Adverse Event Assessment

An assessment of the subjects for adverse events will be performed after the stent removal procedure is completed; see Section 8.

7.2.9 Clinician Satisfaction Survey

Within one working day of each stent removal procedure, the investigator will complete the Clinical Satisfaction Survey to assess her/his satisfaction with the cystoscope on a five-point scale of 1) Exceedingly difficult to 5) Extremely easy. The Survey will evaluate the following attributes:

- Ease of insertion
- Ability to visualize anatomical landmarks and/or urothelium changes
- Perception of image quality
- Maneuverability in the bladder
- Scope articulation with tools in the working channel

In addition, an overall rating of the Ambu® aScope™ 4 Cystoscope as an acceptable instrument/scope option for stent removal procedures will be evaluated.

7.3 Post-procedure AE Assessments (Days 7-10)

On Day 7-10 post-stent removal procedure, study personnel will contact the subject to assess if any adverse events related to the cystoscope procedure and/or study device have occurred; see Section 8. The contact can be done via phone call or a clinic visit, at the discretion of the study personnel performing the assessment and may be performed at any time between Days 7-10 post-procedure.

The subject will be asked if they have had any signs or symptoms of a UTI or any untoward effects post-procedure, including but not limited to gross hematuria lasting longer than three (3) days post-procedure; pain with urination lasting longer than three (3) days post-procedure, cloudy urine noted greater than one day post-procedure; fever/chills or a diagnosis of UTI or other illness within the time since the cystoscopic procedure. A script will be used to guide the discussion with the subject to help ensure the consistent and accurate collection of information. Up to three attempts will be made to reach a subject. An inability to talk with the subject will not be considered an investigational plan deviation.

7.4 Study Completion

A subject's participation in the study will be considered complete once the 7-10 Day post-procedure AE assessment has been completed.

7.5 Suspension or Early Termination

The Sponsor reserves the right to suspend or terminate the study at an individual study site or entirely at any time. Suspension or early termination of a study site may occur due to serious or repeated noncompliance on the part of an investigator. There are no criteria for

termination of the clinical investigation on statistical grounds. Reasons for suspension or early termination of the entire study may include, but are not limited to, the following:

- The incidence and seriousness of AEs in this study indicate a potential health hazard to subjects
- New information on efficacy from this or other studies

In the event of suspension or early termination, the sponsor will promptly inform principal investigators and ensure that IRBs are notified of the stoppage and the reason for it. Subjects must continue to be followed per the protocol unless there is other direction from the sponsor.

8. Adverse Events

8.1 Definitions

The following are definitions and requirements for adverse event monitoring and reporting.

8.1.1 Adverse Event

An adverse event (AE) is any undesirable/unusual medical experience that occurs to a subject during the study regardless of relationship to the study device or procedure. If an investigator is unsure about whether to report a finding as an adverse event, he/she is instructed to report the event in the electronic data capture (EDC) system.

8.1.2 Serious Adverse Event

A serious adverse event (SAE) is an adverse event that:

- Leads to death
- Leads to serious deterioration in the health of a subject that:
  - results in a life-threatening illness or injury,
  - results in permanent impairment of a body structure or body function,
  - requires inpatient hospitalization ≥ 24 hours or prolongation of existing hospitalization,
  - results in medical or surgical intervention to prevent permanent impairment to a body structure or a body function.
  - Leads to fetal distress, fetal death or a congenital abnormality or birth defect.

8.1.3 Anticipated Adverse Events

The risks associated with cystoscopic procedures using endoscopic accessories include but are not limited to the following:

- Intra-procedural pain or discomfort
- Urinary tract infections UTI
- Hematuria
- Abdominal pain
- Dysuria - Pain and discomfort on voiding

- Increase voiding frequency
- Urethral narrowing (strictures) due to scar tissue formation
- Bladder perforation
- Injuries to urethral and bladder tissue from protruding tools
- Abnormal Bleeding
- Inflammation

8.1.4 Adverse Event Reporting - Site

All suspected and known adverse events (see Section 8.1.1) are to be reported in the EDC system in a timely manner (within five working days is recommended) and are to be updated with new information and upon final resolution of the event. Supporting source documents for AEs may be requested by Ambu®; these documents are to be de-identified, labeled with the subject's study identification (ID) number, and uploaded by the site to the EDC system. Additionally, sites are required to report deaths that may be caused by the aScope™ 4 Cystoscope electronically to FDA by completing FDA Form 3500A; see the FDA's website for "Mandatory Summary of Mandatory Reporting Requirements for User Facilities."

Relatedness

Adverse events will be categorized by the investigator as to their relatedness to the study device (aScope™ 4 Cysto System) and/or the stent removal procedure using the following classifications:

- Not Related: The event has no relationship to the study device or procedure.
- Possibly Related: The event has a strong temporal relationship to the study device or procedure and alternative etiology is equally or less likely compared to the potential relationship to the study device or procedure.
- Definitely Related: The event is clearly caused by the study device or procedure and another etiology is unlikely.
- Unknown: Relationship of the event to study device or procedure and alternative etiology is unknown. There is no evidence or relevant data available to assess the relationship between the event and the device or procedure.

Severity

Adverse events will be categorized by the investigator as mild, moderate, or severe, depending on the event's impact on the subject's daily activity level:

- Mild: Usually transient, requiring no special treatment; does not interfere with the subject's daily activities.
- Moderate: Low-level inconvenience or concern to the subject; may interfere with daily activities, usually resolved by simple therapeutic non-interventional methods.

- Severe: Interruption in subject's daily activity requiring systemic drug therapy or other treatment.

8.1.5 Adverse Event Reporting – Sponsor

Ambu Inc. will complete an FDA Form 3500A when it learns that its device may have caused or contributed to a death or serious injury and/or when it becomes aware that its device has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. All adverse events and device deficiencies will also be reported in the final clinical study report.

9. Statistical Methods

9.1 Statistical Hypotheses

The primary objective of demonstrating the stent removal success rate in the aScope™ 4 Cysto arm will be measured by descriptive statistics of the success rate, including 95% confidence intervals. The study hypothesis is that the aScope™ 4 Cysto will perform with a 95% success rate of stent removal procedures.

The null-hypothesis for all other variables will be that the that the value of the endpoint is equal among patients randomized to aScope™ 4 Cysto and patients randomized to the standard flexible cystoscope of the urologist's choice.

9.2 Sample Size

Approximately up to 102 subjects will be enrolled. Subjects will be randomized at a 1:1 ratio for each arm.

9.3 Statistical Test Methods

9.3.1 Primary and Secondary Endpoint Analyses

All continuous variables and all ordered categorical data will be tested by means of the Wilcoxon rank sum test. Binary data will be tested by means of the Fisher's exact test.

All p-values will be 2-sided and nominal p-values will be presented, i.e. no adjustment for multiplicity.

Descriptive statistics, including 95% confidence intervals when applicable, will be presented for each endpoint by group.

9.3.2 Safety Endpoint Analysis

The assessment of safety will include a summary by group of the incidence and seriousness of all reported adverse events through the ten (10) day follow-up assessment including the following:

- Rates of all reported adverse events

- Rates of device-related adverse events
- Rates of procedure-related adverse events

9.4 Other Statistical Considerations

9.4.1 Analysis Sets

- The intention to treat (ITT) analysis set will consist of all enrolled subjects regardless of whether they have undergone a stent removal procedure or follow-up assessment at Day 10.
- The per protocol (PP) analysis set will consist of all enrolled subjects who completed the stent removal procedure and 10-Day assessment. Subjects who are lost to follow-up (and therefore cannot be counted toward any success rates that rely on verifying the absence of any possible post-procedure AEs) will not be included in PP analysis set.

  The PP analysis set will be the primary analysis set and the analyses based on the ITT analysis set will be considered sensitivity analyses.

9.4.2 Pooling Data across Sites

In the statistical analyses data will be pooed between the sites. However, for the primary objective the statistical analysis will be conducted for each site separately as well.

9.4.3 Standard Statistical Methods

Unless otherwise stated, all *P*-values will be nominal and two-sided and considered statistically significant at a significance level of $\alpha = 0.05$. Summary statistics will be generated for all relevant variables. Continuous variables will be summarized with N, mean, median, standard deviation (SD), minimum, and maximum; discrete variables will be summarized with frequency counts and percentages. No corrections will be made for multiple testing procedures, and no imputations for missing data will be applied.

10. Study Administration

10.1 Regulatory Considerations

This post approval study will be conducted under applicable federal regulations and in accordance with applicable elements of 21 CFR Part 11, 21 CFR 50, 54 and 56, ISO 14155 and in accordance with ethical principles that have their origin in the Declaration of Helsinki.

10.2 Institutional Review Board (IRB) Approval

The study must be reviewed and approved by the central or site IRB before subject enrollment begins at the site. Any additional requirements imposed by the IRB will be followed.

Investigators are responsible for submitting and obtaining initial approval and continuing approval from the IRB and uploading copies of the approval letters, associated correspondence and ICF/HIPAA forms to the electronic Trial Master File (eTMF). The investigator will notify Ambu within five (5) working days in the event of withdrawal of IRB approval.

10.3 Clinical Trial Agreement and Financial Disclosure

The investigator agrees to be responsible for conducting this study in accordance with the signed clinical trial agreement and this investigational plan, including study team oversight/management, reporting and record-keeping requirements and controlling the study devices. In addition, the investigator is responsible for ensuring that proper informed consent is obtained from each subject prior to participating in the study as well as protecting the rights, safety and welfare of participating subjects.

All investigators will be required to sign a financial disclosure form, which certifies the investigator's and his/her immediate family's financial interest in the study sponsors and study outcomes. Investigators must inform Ambu of any changes related to financial disclosure throughout the course of the study and for a period of one year after the study is terminated.

10.4 Device Deficiency

All device deficiencies related to the identity, quality, durability, reliability, safety, or performance of the aScope™ 4 Cysto endoscope and the aView™ 2 Advance monitor will be documented by sites on the eCRF throughout the clinical investigation and appropriately managed by the sponsor. Device deficiencies include failures, malfunctions, use errors and inadequate labeling. Device deficiencies will be evaluated by the site investigator for AE potential, that is, if it could have led to an AE under different circumstances.

10.5 Subject Confidentiality

All information and data sent to Ambu, the study sponsor or their designees concerning subjects and their participation in this study are considered confidential by Ambu. Only authorized Ambu personnel or approved contracted agents will have access to confidential files and will act in accordance with applicable regulations as required by HIPAA. The FDA and IRB also have the right to inspect and copy all records pertinent to this study.

10.6 Subject Withdrawal or Discontinuation

Subjects are free to withdraw their consent and stop participating in the clinical investigation at any time without penalty or repercussions of any kind. If a subject expresses the desire to discontinue participation, this must be documented in the subject's research file along with the reason for discontinuation (if provided).

Investigators may discontinue a subject's participation in the investigation for any reason, including:

- The subject is lost to follow-up. For subjects who are lost to follow-up, a minimum of three (3) contact attempts will be documented in the subject's eCRF.
- The subject is non-compliant with study requirements
- Other reasons as determined by the investigator.

10.7 Site Qualification

Investigational site qualification visits or phone calls will be conducted by Ambu prior to acceptance of a site into this study. The site qualification visit/call will be scheduled to include time with the investigator, co-investigators, study coordinator and other study personnel. Individual investigator experience levels and case volumes will be documented for all participating providers. A written report of the qualification visit/call will be written by Ambu.

Resolution of any concerns and/or completion of any necessary activities identified during the visit/call will be documented and submitted to the investigator.

10.8 Site Training

Study-specific training of study personnel is the responsibility of Ambu and the investigator. Study training will occur before first enrollment. To ensure investigational plan compliance as well as accurate data collection, site training will include a detailed review of the investigational plan, eCRF completion, study-specific procedures, aScope™ 4 Cysto endoscope and monitoring logistics. Training on the proper use and disposal of the aScope™ 4 Cysto endoscope will be provided by Ambu personnel.

10.9 Device Accountability

Ambu will provide the aScope™ 4 Cysto and aView 4 Monitors to the sites. All aView 4 Monitors and unused aScope™ 4 Cysto will be returned to Ambu upon the completion of the study. All aScope™ 4 Cysto endoscopes must disposed of in accordance with local guidelines for collection of infected medical devices with electronic components. However, Ambu requests all defective or failing devices be returned to Ambu; contact Ambu for return instructions.

Upon use of an Ambu® aScope™ 4 Cysto, the study coordinator will complete the Device Accountability Log (DAL), documenting use of each device unit by lot number and subject ID for whom it was used. The disposition of each scope will be entered on the DAL and all entries on the DAL must be dated and signed.

10.10 Monitoring and Data Management

This study will be conducted and monitored in accordance with this investigational plan, the study's monitoring plan and Ambu standard operating procedures,

The study site will undergo monitoring visits for evaluation of appropriate conduct and documentation of informed consent, timeliness of data form completion, data accuracy, and investigational plan and regulatory compliance.

The eCRFs will be reviewed for completeness and accuracy at the investigational site and remotely through the Trial Master File (TMF) by Ambu. Information on the eCRFs will be compared to information originally recorded on source documents (i.e. medical record, professional notes, study-specific worksheets, etc.). If information on the CRF does not match the corresponding information on the source document, a data clarification form (DCF) for site resolution will be generated.

The monitor may request further documentation, such as clinic notes or lab reports, when adverse events, complications, or malfunctions are observed and reported.

The site will receive a follow-up letter and/or email regarding action points and corrective actions that must be addressed before the next monitoring visit. Documented site noncompliance will be subject to corrective action. If corrective actions are not undertaken or

are ineffective, the clinical site may be withdrawn from the study by the sponsor Data Management
Study-specific eCRFs will be used to enter study data into the study's EDC system. Designated and trained study personnel at each site are responsible for entering data into the EDC system. Queries will be managed within the EDC system. Prior to final database lock, the investigator will electronically sign the eCRFs; this responsibility cannot be delegated to another person.

Data and eCRFs will be reviewed by Ambu at regular intervals throughout the study as outlined in the study's Monitoring Plan. Queries may be generated by a monitor during a monitoring visit and/or during remote data review. Data management, including queries, will be conducted in accordance with the study's Data Management Plan.

10.11 Trial Master File

This study will utilize a trial master file (TMF, also known as a regulatory binder) for the management of all study-related documents that are required by federal law and good clinical practices. The TMF will be routinely monitored both remotely and during onsite monitoring visits. It is the site's responsibility to ensure all required study documents are complete and filed to the TMF in a timely manner.

10.12 Investigator Responsibilities

The investigator is responsible for ensuring that the study is conducted according to the Clinical Trial Agreement, the investigational plan, IRB requirements and HIPAA. Specific investigator responsibilities are listed in the Clinical Trial Agreement and this investigational plan.

Records and reports must remain on file at the investigational site for a minimum of ten years after the completion/termination of this study. They may be discarded only upon written approval from the sponsor. The sponsor must be contacted if the investigator plans to leave the site to ensure that arrangements for a new investigator or records transfer are made prior to the investigator's departure.

10.13 Investigator Records

Records to be maintained by the investigator may include, but are not limited to:

- Investigational plan and all amendments
- Signed Clinical Trial Agreement
- Signed Financial Disclosure Forms
- IRB approval letter including consent and HIPAA authorization form(s)
- IRB Membership List or Letter of Assurance
- All correspondence relating to the study between the site and study sponsors and/or Ambu
- *Curriculum vitae* (CVs) and professional licenses for all investigators and licensed study clinicians.
- Site personnel signature and responsibility list
- Clinical monitor sign-in log
- Subject screening log
- The following records will be maintained for each subject enrolled in the study:

- Subject-signed ICFs and HIPAA forms and documentation of the consenting process
- Complete, accurate and current source documentation for eCRFs
- Adverse event reports and any supporting documentation
- Investigational plan deviations
- Complete medical records relative to the study

10.14 Investigator Reports

See Section 8.1.5 for specific requirements for reporting AEs and device problems to the sponsor via the EDC system and FDA via electronic submission of Form 3500A. The investigator is required to follow applicable IRB reporting requirements. The investigator is required to notify the sponsor of withdrawal of IRB approval within five working days and to submit annual study progress reports to the IRB and sponsor. An investigator shall notify the sponsor and IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but not later than five working days after the emergency occurs.

10.15 Investigational Site Termination

The sponsor may terminate an investigational site for any of the following reasons:

- Failure to secure subject informed consent or HIPAA authorization prior to enrollment
- Failure to properly report adverse events, according to regulatory and/or IRB requirements
- Repeated investigational plan violations
- Failure to enroll an adequate number of subjects
- Administrative decision by the company

10.16 Sponsor Records

The sponsor will maintain the following records:

- Investigational plan and all amendments.
- Signed Clinical Trial Agreements.
- Institutional Review Board approval letters, including a copy of the approved consent form(s).
- All correspondence relating to this study between the Sponsor the investigational site, IRB, and FDA.
- CVs for all study personnel.
- Site personnel signatures and responsibility lists.
- Investigational device inventory log including date, quantity, and lot numbers of devices shipped to and returned by the sites.

10.17 Sponsor Reports

- Required adverse event and device deficiency reports will be submitted electronically to FDA on Form 3500A.
- Withdrawal of an IRB's approval to other IRBs and investigators – five (5) working days.
- Final Study Report

10.18 Investigational Plan Amendments

Investigators may not modify this investigational plan. The sponsor may amend this investigational plan during the study, and such amendments will be submitted to the IRBs by the sites for approval.

10.19 Investigational Plan Deviations

Investigators shall not intentionally deviate from the current approved investigational plan without approval from the sponsor except to protect the life or physical well-being of a subject in an emergency situation. Such deviations will be reported to the sponsor and to the site's governing IRB within two working days. All investigational plan deviations must be reported in the EDC system on the Protocol Deviation eCRF. The study sponsor may terminate investigator participation in the event of significant and/or continued non-compliance with the investigational plan.

10.20 Publication and Registration

Ambu will communicate and/or publish results from this study, including results from interim analyses, at its discretion. The study will be registered on ClinicalTrials.gov.

11. Revision History

Version	Approval Date	Description of Change	Brief Rationale
2		Primary Objective/Endpoint changed to the stent success rate of the Ambu arm. CPT comparison between the two arms was added as secondary endpoint. Total sample size reduced from 170 subjects to up to 102 subjects. Additional administrative and format changes.	The study design was altered to be more aligned with a validation study to evaluate the comparison results as there are no predicate studies to support the statistically powered hypothesis. Formatting and administrative changes were performed to ensure consistency throughout the protocol.

12. Bibliography

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